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PTO/SB/21 (04-04)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/057,534
Filing Date	January 25, 2002
First Named Inventor	Harry R. Davis et al.
Art Unit	1617
Examiner Name	Shengjun Wang
Total Number of Pages in This Submission: 38	Attorney Docket Number: CV001378K US – 4686-048002

ENCLOSURES (Check all that apply)

- ☒ Fee Transmittal Form
  - ☒ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Documents
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition to Reinstate
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s)_____
- ☐ After Allowance communication To Technology Center (TC)
- ☐ Appeal Communication to Board Of Appeals and Interferences
- ☒ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please identify below)

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Or Individual name	Ann M. Cannoni Webb Ziesenheim Logsdon Orkin & Hanson, P.C.
Signature	
Date	August 2, 2005

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being sent via Express Mail to the USPTO or deposited with the United States Postal Service with sufficient postage in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Chris Craig		
Signature	Chris Craig	Date	August 2, 2005

PTO/SB/17 (12-04)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818)

FEE TRANSMITTAL for FY 2005

[ ] Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 500.00

Complete if Known	
Application Number	10/057,534
Filing Date	January 25, 2002
First Named Inventor	Harry R. Davis, et al.
Examiner Name	Shengjun Wang
Art Unit	1617
Attorney Docket No.	CV01378K/4686-048002

METHOD OF PAYMENT (check all that apply)

[X] Check [ ] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[ ] Deposit Account Deposit Account Number: 23-0650 Deposit Account Name The Webb Law Firm

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

[ ] Charge fee(s) indicated below
[ ] Charge fee(s) indicated below, **except for the filing fee**
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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 20 or HP =	_____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____ (round up to a whole number)	x _____	= _____

4. OTHER FEE(S)

	Fee Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other: Appeal Brief	500.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 35,972	Telephone 412-471-8815
Name (Print/Type)	Ann M. Cannoni		Date August 2, 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re:	Patent Application of Harry R. Davis et al.	: PATENT APPLICATION
Serial No.:	10/057,534	: Group Art Unit: 1617
Filed:	January 25, 2002	: Examiner: Shengjun Wang
For:	Combinations of Bile Acid Sequestrant(s) and Sterol Absorption Inhibitor(s) and Treatments for Vascular Indications	: Atty. Docket No.: CV01378K

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ON APPEAL FROM THE PRIMARY EXAMINER TO THE
BOARD OF PATENT APPEALS AND INTERFERENCES

08/04/2005 EFLORES 00000064 10057534
01 FC:1402 500.00 OP

APPELLANT'S BRIEF UNDER 37 C.F.R. § 1.192

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August 2, 2005 Chris Craig
Date Signature

Chris Craig
Typed Name of Person Signing Certificate

TABLE OF CONTENTS

I

REAL PARTY IN INTEREST

The real party in interest in this Appeal is assignee Schering Corporation, having a principal place of business 2000 Galloping Hill Road, Kenilworth, NJ 07033.

II

RELATED APPEALS AND INTERFERENCES

As the legal representative of Appellant, the undersigned attorney has no knowledge of any appeals or interferences directly related to this Appeal.

III

STATUS OF CLAIMS

This is an original patent application in which claims 1-3, 5, 6, 8-28, 31-36, 70-72, 74-77, 79 and 80 are pending in this application. Claims 4, 29, 30, 37-69, 73, 78 and 81 have been withdrawn from consideration by the Examiner as being non-elected. Claim 7 was canceled, without prejudice to filing one or more related applications directed to the canceled subject matter thereof.

Claims 1-3, 5, 6, 8-28, 31-36, 70-72, 74-77, 79 and 80 (pending) were finally rejected under 35 U.S.C. §103(a) in an Office Action mailed March 24, 2005 ("Final Office Action") and Advisory Action mailed June 15, 2005 ("Advisory Action").

Forty-one (41) pending claims (1-3, 5, 6, 8-28, 31-36, 70-72, 74-77, 79 and 80) are at issue in this Appeal.

IV

STATUS OF AMENDMENTS

No claims were amended after final rejection. A copy of the claims involved in this Appeal is contained in the Appendix attached hereto.

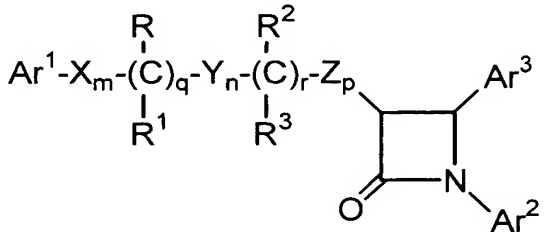
V

SUMMARY OF CLAIMED SUBJECT MATTER

In embodiments set forth in claim 1, Applicants have discovered compositions comprising:

(a) at least one bile acid sequestrant; and

(b) about 10 milligrams of at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5

or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

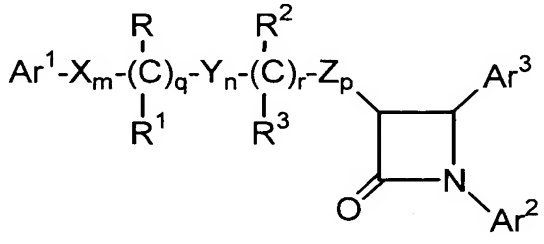
R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

See original claim 1, page 3, line 1 through page 4, line 11 and page 82, line 13 of the specification.

In other embodiments set forth in Claim 31, Applicants have discovered therapeutic combinations comprising:

(a) a first amount of at least one bile acid sequestrant; and

(b) a second amount of about 10 milligrams of at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$,

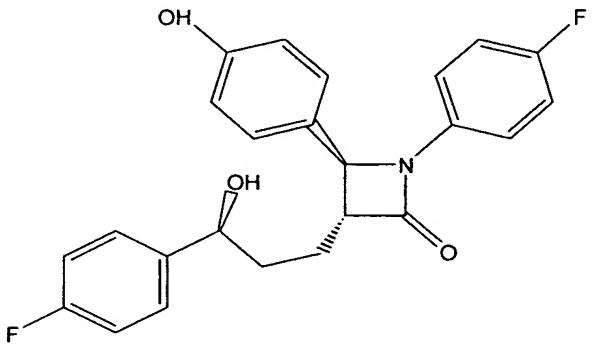
$-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal. See original claim 31, and page 22, line 27 through page 23, line 6 of the specification.

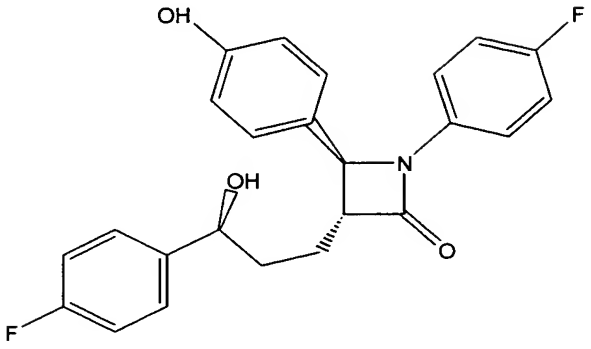
In other embodiments set forth in Claim 35, Applicants have discovered compositions comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of a compound represented by Formula (II) below:



(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof. See original claim 35, and page 4, line 12-17 of the specification.

In other embodiments set forth in Claim 36, Applicants have discovered therapeutic combinations comprising: (a) a first amount of at least one bile acid sequestrant; and (b) a second amount of about 10 milligrams of a compound represented by Formula (II) below:



(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal. See original claim 36, and page 22, line 27 through page 23, line 6 of the specification.

In other embodiments set forth in Claim 70, Applicants have discovered compositions comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of at least one substituted azetidinone compound or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the at least one substituted azetidinone compound or of the isomers, salts or solvates thereof. See original claim 70, and page 22, lines 18-26 of the specification.

In other embodiments set forth in Claim 76, Applicants have discovered compositions comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of at least one substituted β-lactam compound or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof.. See original claim 76, and page 22, lines 18-26 of the specification.

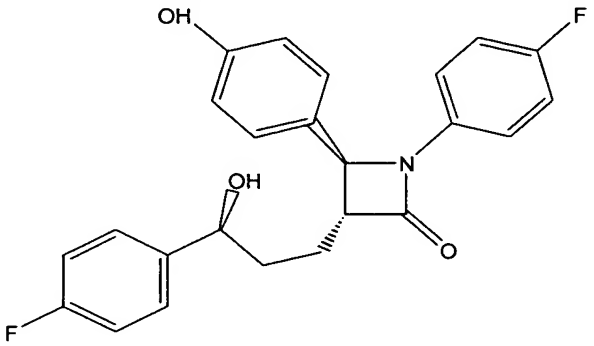
In other embodiments set forth in Claim 79, Applicants have discovered therapeutic combinations comprising:

(a) a first amount of at least one bile acid sequestrant; and

(b) a second amount of about 10 milligrams of at least one substituted β-lactam compound or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof,
wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal. See original claim 79.

In the Office Action of July 16, 2003, Applicants were required to elect a species of sterol absorption inhibitor, a species of bile acid sequestrant, and a third agent listed in claims 8-27.

Applicants provisionally elected with traverse ezetimibe as the sterol absorption inhibitor, represented by Formula (II) below:



(II).

Ezetimibe is the active ingredient in ZETIA™ (ezetimibe) pharmaceutical formulation and VYTORIN™ (ezetimibe/simvastatin) pharmaceutical formulation, both of which are commercially available from MSP (Merck Schering-Plough) Pharmaceuticals, Inc. See Response to Restriction Requirement and Election of Species of ("Restriction and Election Response") at page 2, lines 11-13.

Applicants provisionally elected with traverse cholestyramine as the bile acid sequestrant for initial examination in the application. See Restriction and Election Response at page 2, lines 7-10.

Applicants provisionally elected with traverse simvastatin as the third agent for initial examination in the application. See Restriction and Election Response at page 2, lines 14-17.

The claimed compositions and combinations can be useful for treating or preventing a vascular condition, diabetes, obesity and/or lowering concentration of a sterol or 5α-stanol in plasma in a subject (page 23, lines 11-14 of the specification).

VI

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Has a Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over Claims 1-3, 5-28, 31-36, 70-72, 74-77, 79 and 80 as obvious over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of U.S. Patent No. 5,300,288 ("Albright"), U.S. Patent No. 4,837,255 ("Dechow") and U.S. Patent No. 5,661,145 ("Davis") Been Established?

VII

ARGUMENT

I. The Required Prima Facie Case of Obviousness of Claims 1-3, 5-28, 31-36, 70-72, 74-77, 79 and 80 Under 35 U.S.C. § 103 Over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of U.S. Patent No. 5,300,288 ("Albright"), U.S. Patent No. 4,837,255 ("Dechow") and U.S. Patent No. 5,661,145 ("Davis") has Failed to be Established.

A. The Rejection

Claims 1-3, 5-28, 31-36, 70-72, 74-77, 79 and 80 have been rejected as obvious over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of U.S. Patent No. 5,300,288 ("Albright"), U.S. Patent No. 4,837,255 ("Dechow") and U.S. Patent No. 5,661,145 ("Davis").

The reasons for rejection are set forth in the Final Office Action, summarized as follows:

It is asserted that Rosenblum et al. teach the instant cholesterol absorption inhibitors, their application for lowering serum cholesterol and combination with other cholesterol lowering agents such as simvastatin. Final Office Action at page 2. Further, it is asserted that Rosenblum et al, teach a

daily dosage in a range of 5 mg to 1000 mg a dose given 1 or two times a day and that the exact dose would depend upon various conditions. Final Office Action at page 2.

It is acknowledged that Rosenblum et al. do not expressly teach a combination of a hydroxyl substituted azetidinone, such as ezetimibe, and a bile acid sequestrant, e.g., cholestyramine, or further with a cholesterol biosynthesis inhibitor, e.g. simvastatin. Final Office Action at page 2.

It is alleged that Albright discloses that cholestyramine is an old and well-known cholesterol lowering agent and that Dechow teaches a method of lowering cholesterol by administering cholestyramine. Final Office Action at pages 2-3.

It is alleged that it would have been obvious to one of ordinary skill in the art, at the time that the claimed invention was made, to make a cholesterol lowering composition comprising hydroxyl substituted azetidinone, e.g., ezetimibe, and the well known cholesterol lowering agent cholestyramine, citing In re Kerkoven, 205 U.S.P.Q. 1069. Final Office Action at page 3.

It is further alleged that optimization of a result-effective parameter, e.g., effective amount of a therapeutic agent, is within the skill of the artisan, citing In re Boesch and Slaney, 204 U.S.P.Q. 215, and that the specific amount of 10 mg is within the range disclosed by Rosenblum et al..

B. The Prior Art

Rosenblum et al. disclose cholesterol absorption inhibitors, their application for lowering serum cholesterol and combination with simvastatin. Rosenblum et al. do not teach a combination of a hydroxyl substituted azetidinone, such as ezetimibe, and a bile acid sequestrant, e.g., cholestyramine, or further with a cholesterol biosynthesis inhibitor, e.g. simvastatin. Albright discloses that cholestyramine is a cholesterol lowering agent and Dechow teaches a method of lowering cholesterol by administering cholestyramine.

C. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

The law is replete with cases holding that there must be some suggestion or motivation in the prior art to combine the references. When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).

The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious *unless the prior art suggests the desirability of the modification* (emphasis added). In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due

consideration to the persuasiveness of any arguments and any secondary evidence." Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Claims 1-3, 5, 6, 28, 31-36, 70-72, 74-77, 79 and 80

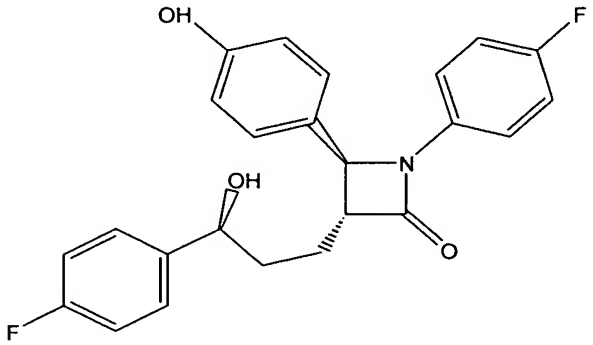
Claims 1 and 31 recite a composition and therapeutic combination, respectively, comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of at least one sterol absorption inhibitor represented by Formula (I) above.

Claim 2 depends from claim 1 and further recites that the bile acid sequestrant is selected from the group consisting of cholestyramine, colestipol, colesevelam hydrochloride and mixtures thereof.

Claim 3 depends from claim 2 and further recites that the bile acid sequestrant comprises cholestyramine.

Claim 5 depends from claim 1 and further recites that the bile acid sequestrant is administered to a mammal in an amount ranging from about 1 to about 50 grams of bile acid sequestrant per day

Claim 6 depends from claim 1 and further recites that the sterol absorption inhibitor is represented by Formula (II) below:



(II)

or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof.

Claim 28 depends from claim 1 and further recites a pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes,

obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 1 and a pharmaceutically acceptable carrier.

Claim 32 depends from claim 1 and further recites that the bile acid sequestrant is administered concomitantly with the at least one sterol absorption inhibitor.

Claim 33 depends from claim 1 and further recites that the bile acid sequestrant and the at least one sterol absorption inhibitor are present in separate treatment compositions.

Claim 34 depends from claim 1 and further recites a method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the therapeutic combination of claim 31.

Claims 32 and 36 recite a composition and a therapeutic combination, respectively, comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of a compound represented by Formula (II) or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof.

Claim 70 recites a composition comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of at least one substituted azetidinone compound or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the at least one substituted azetidinone compound or of the isomers, salts or solvates thereof.

Claim 71 depends from claim 70 and recites a pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 70 and a pharmaceutically acceptable carrier.

Claim 72 depends from claim 70 and recites a method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration

of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the composition of claim 70.

Claim 74 recites a pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 73 and a pharmaceutically acceptable carrier.

Claim 75 recites a method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the composition of claim 73.

Claims 76 and 79 recite a composition or a therapeutic combination, respectively, comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of at least one substituted β-lactam compound or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof.

Claims 77 and 80 depend from claims 76 and 79, respectively, and recite a pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the compositions of claim 76 and 79, respectively, and a pharmaceutically acceptable carrier.

It is respectfully submitted that the combination of the references cited by the Examiner as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of about 10 milligrams of sterol absorption inhibitor (such as ezetimibe) and cholestyramine.

In the In re Kerkoven case cited by the Examiner, the Court found the motivation or suggestion to combine two materials each disclosed in a separate reference from the fact that each reference taught the individual materials for the very same purpose as in the claimed combination. That is not the situation here.

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. See ZETIA™ (ezetimibe) Tablets Package Insert at column 1 (Merck/Schering-Plough Pharmaceuticals) (October 2002) included in the Information Disclosure Statement filed January 15, 2004.

The cholesterol content of the liver is derived predominantly from three sources. Id. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Id. Intestinal cholesterol is derived primarily from cholesterol secreted in the bile and from dietary cholesterol. Id.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (HMG CoA reductase inhibitors, bile acid sequestrants (resins), fibric acid derivatives, and plant stanols). Id.

Ezetimibe does not inhibit cholesterol synthesis in the liver (like HMG CoA reductase inhibitors), or increase bile acid excretion (like bile acid sequestrants). Id. Instead, ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. Id. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG CoA reductase inhibitors. Id.

Ezetimibe does not operate by the same mechanism as either cholestyramine or cholesterol biosynthesis inhibitors. Because of the difference of the way that each component of the presently claimed combination acts, it is respectfully submitted that the rejection is based upon an improper combination of references. There is no suggestion or motivation in the references to combine the claimed components that operate by these

different mechanisms. One skilled in the art would understand that the compatibility and efficacy of drug combinations can be unpredictable.

It is impermissible to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *No motivation has been provided to select these two particular types of lipid management compounds out of numerous lipid management compounds.*

Further, *there is no motivation to select the claimed amount of about 10 milligrams* of sterol absorption inhibitor (such as ezetimibe). In re Boesch and Slaney relates to a nickel based alloy composition, not administration of a therapeutic agent to a human that is less predictable.

If the above teachings were combined as proposed in the Office Action, there is no motivation to select the claimed combination of a sterol or stanol absorption inhibitor (such as ezetimibe) and a bile acid sequestrant.

Claims 8-27

Claims 8-27 depend directly or indirectly from claim 1, and further recite additional active components.

Claim 8 recites that the composition of claim 1 further comprises at least one cholesterol biosynthesis inhibitor. Claim 9 depends therefrom and recites that the at least one cholesterol biosynthesis inhibitor comprises at least one HMG CoA reductase inhibitor. Claim 10 depends therefrom and recites that the at least one HMG CoA reductase inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, cerivastatin and mixtures thereof. Claim 11 depends therefrom and recites that the at least one HMG CoA reductase inhibitor is simvastatin.

Claim 12 recites that the composition of claim 1 further comprises at least one PPAR receptor activator. Claim 13 depends from claim 12 and recites that the PPAR receptor activator is at least one fibric acid derivative is selected from the group consisting of fenofibrate, clofibrate, gemfibrozil, ciprofibrate, bezafibrate, clinofibrate, binifibrate, lifibrol and mixtures thereof.

Claim 14 depends from claim 13 and recites that the at least one fibric acid derivative is fenofibrate.

Claim 15 depends from claim 1 and recites that the composition further comprises nicotinic acid or a derivative thereof.

Claim 16 depends from claim 1 and recites that the composition further comprises at least one AcylCoA:Cholesterol *O*-acyltransferase Inhibitor.

Claim 17 depends from claim 1 and recites that the composition further comprises probucol or derivatives thereof.

Claim 18 depends from claim 1 and recites that the composition further comprises at least one low-density lipoprotein receptor activator.

Claim 19 depends from claim 1 and recites that the composition further comprises at least one Omega 3 fatty acid.

Claim 20 depends from claim 1 and recites that the composition further comprises at least one natural water soluble fiber.

Claim 21 depends from claim 1 and recites that the composition further comprises at least one of plant sterols, plant stanols or fatty acid esters of plant stanols.

Claim 22 depends from claim 1 and recites that the composition further comprises at least one antioxidant or vitamin.

Claim 23 depends from claim 1 and recites that the composition further comprises at least one hormone replacement therapy composition.

Claim 24 depends from claim 1 and recites that the composition further comprises at least one obesity control medication.

Claim 25 depends from claim 1 and recites that the composition further comprises at least one blood modifier different from the compound of Formula (I).

Claim 26 depends from claim 1 and recites that the composition further comprises at least one cardiovascular agent different from the compound of Formula I.

Claim 27 depends from claim 1 and recites that the composition further comprises at least one antidiabetic medication.

It is respectfully submitted that the combination of the references cited by the Examiner as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of about 10 milligrams of sterol absorption inhibitor (such as ezetimibe), cholestyramine, and other active component of claims 8-27 above.

In the In re Kerkoven case cited by the Examiner, the Court found the motivation or suggestion to combine two materials each disclosed in a separate reference from the fact that each reference taught the individual materials for the very same purpose as in the claimed combination. That is not the situation here.

As stated above, ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (HMG CoA reductase inhibitors, bile acid sequestrants (resins), fibric acid derivatives, and plant stanols). Id. Ezetimibe does not operate by the same mechanism as either cholestyramine or cholesterol biosynthesis inhibitors. Because of the difference of the way that each component of the presently claimed combination acts, it is respectfully submitted that the rejection is based upon an improper combination of references. There is no suggestion or motivation in the references to combine the claimed components that operate by these different mechanisms.

Further, hormone replacement therapy, obesity control medications, antidiabetic medications, blood modifier and other carvdiovascular agents as set forth above are not generally known for lowering cholesterol, therefore In re Kerkoven does not apply.

Claim 23 depends from claim 1 and recites that the composition further comprises at least one hormone replacement therapy composition. Applicants note that claims to a composition or therapeutic combination of at least one hormone replacement therapy and at least one sterol or 5α stanol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof have been allowed in U.S. Patent Application Serial No. 10/247,085. Also allowed is dependent claim 26 of that application which recites that the composition further comprises a bile acid sequstrant.

Claim 24 depends from claim 1 and recites that the composition further comprises at least one obesity control medication. Applicants note that claims to a composition or therapeutic combination of at least one obesity control medication and at least one sterol or 5α stanol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof have been allowed in U.S. Patent Application Serial No. 10/247,397.

Claim 27 depends from claim 1 and recites that the composition further comprises at least one antidiabetic medication. Applicants note that claims to a composition or therapeutic combination of at least one antidiabetic medication selected from the group consisting of sulfonylurea, meglitinide, biguanide, thiazolidinedione, alpha-glucosidase inhibitor; peptide for increasing insulin production, and combinations thereof for reducing blood glucose levels in a subject, and at least one sterol or 5α stanol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof have been allowed in U.S. Patent Application Serial No. 10/247,099.

It is impermissible to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *No motivation has been provided to select a sterol or 5αstanol absorption inhibitor, bile acid sequetrant and third component as set forth in claims 8-27 above.* If the above teachings were combined as proposed in the Office Action, there is no motivation to select the claimed combination of a sterol or stanol absorption inhibitor (such as ezetimibe) and a bile acid sequestrant.

Further, *there is no motivation to select the claimed amount of about 10 milligrams* of sterol absorption inhibitor (such as ezetimibe). In re Boesch and Slaney relates to a nickel based alloy composition, not administration of a therapeutic agent to a human that is less predictable.

Applicants respectfully assert that the rejection is based upon improper hindsight reconstruction. The prima facie case of obviousness has not been established. Accordingly, Applicants respectfully request that the § 103(a) rejection of claims 1-3, 5-28, 31-36, 70-72, 74-77, 79 and 80 be reconsidered and withdrawn.

Respectfully submitted,

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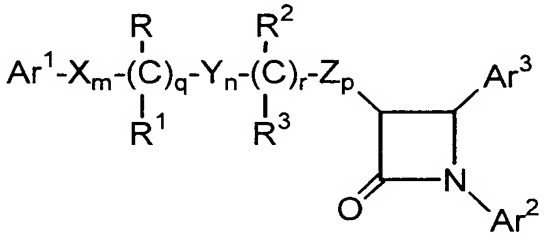
CLAIM APPENDIX

1. A composition comprising:

(a) at least one bile acid sequestrant; and

(b) about 10 milligrams of at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5

or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

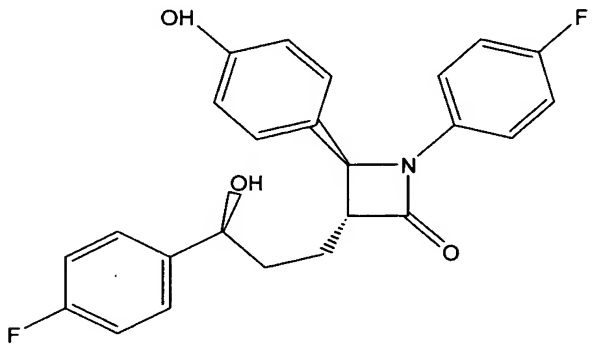
R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

2. The composition according to claim 1, wherein the at least one bile acid sequestrant is selected from the group consisting of cholestyramine, colestipol, colesevelam hydrochloride and mixtures thereof.

3. The composition according to claim 2, wherein the at least one bile acid sequestrant comprises cholestyramine.

5. The composition according to claim 1, wherein the at least one bile acid sequestrant is administered to a mammal in an amount ranging from about 1 to about 50 grams of bile acid sequestrant per day.

6. The composition according to claim 1, wherein the sterol absorption inhibitor is represented by Formula (II) below:



(II)

or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof.

8. The composition according to claim 1, further comprising at least one cholesterol biosynthesis inhibitor.

9. The composition according to claim 8, wherein the at least one cholesterol biosynthesis inhibitor comprises at least one HMG CoA reductase inhibitor.

10. The composition according to claim 9, wherein the at least one HMG CoA reductase inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, cerivastatin and mixtures thereof.

11. The composition according to claim 10, wherein the at least one HMG CoA reductase inhibitor is simvastatin.

12. The composition according to claim 1, further comprising at least one PPAR receptor activator.

13. The composition according to claim 12, wherein the PPAR receptor activator is at least one fibric acid derivative is selected from the group consisting of fenofibrate, clofibrate, gemfibrozil, ciprofibrate, bezafibrate, clinofibrate, binifibrate, lifibrol and mixtures thereof.

14. The composition according to claim 13, wherein the at least one fibric acid derivative is fenofibrate.

15. The composition according to claim 1, further comprising nicotinic acid or a derivative thereof.

16. The composition according to claim 1, further comprising at least one AcylCoA:Cholesterol *O*-acyltransferase Inhibitor.

17. The composition according to claim 1, further comprising probucol or derivatives thereof.

18. The composition according to claim 1, further comprising at least one low-density lipoprotein receptor activator.

19. The composition according to claim 1, further comprising at least one Omega 3 fatty acid.

20. The composition according to claim 1, further comprising at least one natural water soluble fiber.

21. The composition according to claim 1, further comprising at least one of plant sterols, plant stanols or fatty acid esters of plant stanols.

22. The composition according to claim 1, further comprising at least one antioxidant or vitamin.

23. The composition according to claim 1, further comprising at least one hormone replacement therapy composition.

24. The composition according to claim 1, further comprising at least one obesity control medication.

25. The composition according to claim 1, further comprising at least one blood modifier different from the compound of Formula (I).

26. The composition according to claim 1, further comprising at least one cardiovascular agent different from the compound of Formula I.

27. The composition according to claim 1, further comprising at least one antidiabetic medication.

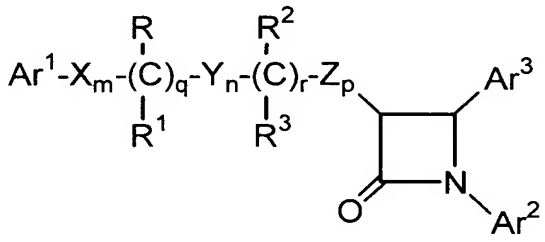
28. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol

in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 1 and a pharmaceutically acceptable carrier.

31. A therapeutic combination comprising:

(a) a first amount of at least one bile acid sequestrant; and

(b) a second amount of about 10 milligrams of at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl

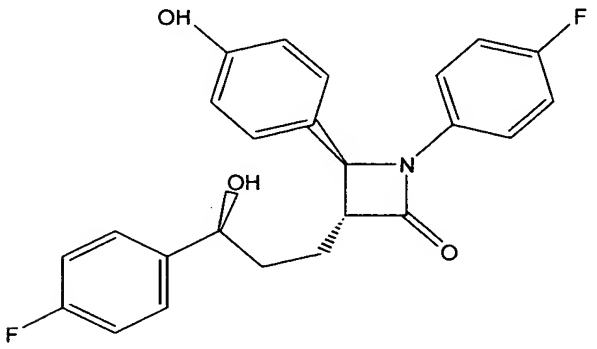
wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

32. A therapeutic combination according to claim 31, wherein the at least one bile acid sequestrant is administered concomitantly with the at least one sterol absorption inhibitor.

33. A therapeutic combination according to claim 31, wherein the at least one bile acid sequestrant and the at least one sterol absorption inhibitor are present in separate treatment compositions.

34. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effecti ve amount of the therapeutic combination of claim 31.

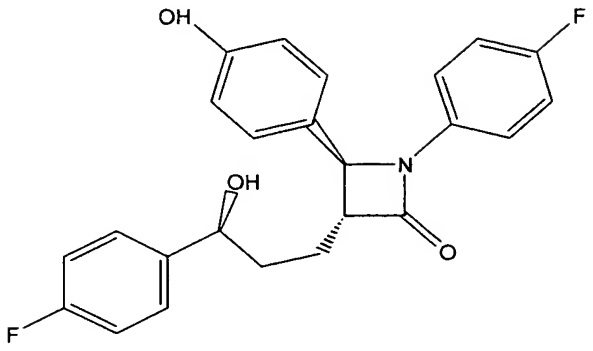
35. A composition comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of a compound represented by Formula (II) below:



(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof.

36. A therapeutic combination comprising: (a) a first amount of at least one bile acid sequestrant; and (b) a second amount of about 10 milligrams of a compound represented by Formula (II) below:



(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

70. A composition comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of at least one substituted azetidinone compound or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the at least one substituted azetidinone compound or of the isomers, salts or solvates thereof.

71. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 70 and a pharmaceutically acceptable carrier.

72. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the composition of claim 70.

74. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol

in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 73 and a pharmaceutically acceptable carrier.

75. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the composition of claim 73.

76. A composition comprising: (a) at least one bile acid sequestrant; and (b) about 10 milligrams of at least one substituted β-lactam compound or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof.

77. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 76 and a pharmaceutically acceptable carrier.

79. A therapeutic combination comprising:

(a) a first amount of at least one bile acid sequestrant; and

(c) a second amount of about 10 milligrams of at least one substituted β-lactam compound or a pharmaceutically acceptable salt or solvate thereof, or prodrug of the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof,

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular

condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

80. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 79 and a pharmaceutically acceptable carrier.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.